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ABSTRACT

This paper is designed to inform program managers and others who are interested in learning more about human immunodeficiency virus (HIV) and infant feeding but who are not necessarily familiar with all of the technical issues in either of these fields. The paper reviews the major advances in the study of human immunodeficiency virus (HIV) and infant feeding and the policy responses to these findings; describes several design and interpretation issues to take into consideration when reading and comparing research studies on this issue; reports the findings of several studies and mathematical models which have been developed to guide program and policy recommendations on HIV and infant feeding; summarizes what existing studies do and do not reveal about this issue; and recommends areas requiring further research to facilitate adaptation and application of the UNAIDS/UNICEF/WHO guidelines on HIV and infant feeding. (Contains 78 references, 2 boxes, and 2 tables.) (SM)

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HIV and Infant Feeding: A Chronology of Research and Policy Advances and their Implications for Programs

Elizabeth A. Preble, MPH
Ellen G. Piwoz, ScD, MHS

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HIV AND INFANT FEEDING:
A CHRONOLOGY OF RESEARCH AND POLICY ADVANCES AND THEIR IMPLICATIONS FOR PROGRAMS

September, 1998

Elizabeth A. Preble, MPH[a]
Ellen G. Piwoz, ScD, MHS[b]

[a] Consultant, LINKAGES Project, Academy for Educational Development
[b] Nutrition Advisor, The Support for Analysis and Research in Africa (SARA) Project, Academy for Educational Development

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The LINKAGES Project
The Support for Analysis and Research in Africa (SARA) Project
Academy for Educational Development
1825 Connecticut Avenue, NW
Washington DC, 20009
Tel: 202-884-8000
Fax: 202-884-8977 USA
E-mail: linkages@aed.org
sara@aed.org

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Executive Summary

Since the mid-1980s, when human immunodeficiency virus (HIV) was detected in breastmilk and cases of HIV transmission to infants during breastfeeding were documented, health policymakers and program managers have struggled to develop appropriate and feasible guidelines on infant feeding for mothers living in settings where HIV is present. Over the past decade, many studies have been carried out to improve our understanding of the HIV-breastfeeding relationship. Several studies have estimated the contribution of postpartum transmission during breastfeeding to the broader spectrum of mother-to-child transmission, which includes transmission before and during delivery. Mathematical models have also been developed to try to compare the risks of mother-to-child transmission of HIV with the additional mortality caused by alternative feeding practices.

The findings of these studies generated a general consensus on these facts: 1) HIV can be found in the breastmilk of HIV-infected mothers; 2) HIV can be transmitted to infants by breastfeeding; and 3) mothers who themselves become infected while breastfeeding are at heightened risk of transmitting the virus to their infants. The studies, however, do not lead directly to clear policy and program guidance for mothers living in resource-poor settings where HIV is prevalent because many critical questions about HIV and infant feeding still remain unanswered. These unanswered questions exist because of limitations in HIV test technology, which make it impossible to determine the precise timing or mode of transmission to newborns at the time of delivery and during the first two months of life, and because of other issues related to the design, analysis, and interpretation of studies on this issue. Also, the mortality and other risks associated with artificial feeding in different environments are largely unknown.

In mid-1998, UNAIDS, UNICEF, and WHO released guidelines on HIV and infant feeding for decision makers, and for health care managers and supervisors. For the first time, the recommendation to provide HIV-seropositive mothers who decide not to breastfeed with replacement feeds has been formally introduced by these organizations. However, the unanswered questions mentioned above leave major gaps in our knowledge and pose major challenges to the adaptation of these guidelines to specific settings and/or to the circumstances of specific mothers, and to the timely, appropriate, and widespread application of these guidelines in countries and communities where HIV exists.

This paper has five major goals with respect to this important issue. These goals are to: 1) review the major advances in the study of HIV and infant feeding and the policy responses to these findings; 2) describe several design and interpretation issues to take into consideration when reading and comparing research studies on this issue; 3) report the findings of several studies and mathematical models which have been developed to guide program and policy recommendations on HIV and infant feeding; 4) summarize what existing studies do and do not reveal about this issue; and 5) recommend areas requiring further research to facilitate adaptation and application of the UNAIDS/UNICEF/WHO guidelines on HIV and infant feeding. The paper is intended to inform program managers and others who are interested in learning more about HIV and infant feeding but who are not necessarily familiar with all of the technical issues in either of these fields.

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I. Introduction

In the mid-1980s, human immunodeficiency virus (HIV) was cultured from breastmilk in HIV-infected mothers, and cases were reported of breastfed infants (of HIV-infected mothers) seroconverting during the postpartum period. This raised concern about the potential of breastfeeding to present a significant risk of mother-to-child transmission of HIV (also referred to as vertical transmission), and possibly a threat to the practice of breastfeeding by both infected and uninfected mothers. This threat was particularly grave, since child survival experts have come to understand the significant benefits that breastfeeding conveys to mothers and infants alike. Breastfeeding, in addition to its nutritional excellence, provides psychological and child-spacing benefits to infants and mothers, and reduces infant and child morbidity and mortality by protecting children from diarrhoeal diseases, pneumonia, and other infections.

After the initial case reports, additional case reports emerged. Data on breastfeeding patterns were culled from earlier mother-to-child transmission studies, and new studies were undertaken on the HIV-breastfeeding relationship. By the late 1990s, a large body of literature was available. However, most of the literature analyzed the same few studies, and/or was based on speculation about a number of biological mechanisms related to transmission via breastfeeding that remained untested. Today, the literature on this subject includes early case reports; studies that estimate the timing of HIV transmission and identify risk factors associated with transmission; observational studies that compare HIV transmission rates in non-breastfed versus partially-breastfed infants; studies that examine HIV concentrations in breastmilk samples; and several mathematical models that estimate mortality risks associated with different feeding patterns in populations with different assumed characteristics.

Perceptions of how serious the problem of HIV transmission through breastfeeding really is, and hence, how strenuously breastfeeding should be defended or discouraged in various settings depends on how one presents existing data, and presentations have varied greatly. For example, all of the following statements concerning breastfeeding risks are accurate based on currently available data:

- Only one to two percent of all HIV transmission occurs through breastfeeding (Labbok, 1997).
- Of seven children born to an HIV-seropositive mother: one will be infected through breastfeeding, two to three will be infected through in-utero or intrapartum transmission, and three to four will remain uninfected (whether or not the mother is breastfeeding) (DeVincenzi, 1997).
- An estimated one-third to one-half of all mother-to-child transmission of HIV worldwide (Kreiss, 1997) and in Africa (Ekpini et al, 1997; Simonon et al, 1994) is due to breastfeeding.
- Fourteen percent of children who are breastfed by a mother who was infected *before* delivery and 29 percent of children who are breastfed by a mother who was infected *after* delivery will become HIV-infected through breastfeeding (Dunn et al, 1992).

Researchers and policy makers have interpreted the same data on risks of HIV transmission through breastfeeding differently, depending on the outcome they are interested in. The first statement, for example, concerns the relative contribution of breastfeeding to *all new cases* of HIV infection. The second statement looks at the expected infection status of *breastfed infants born to HIV-infected mothers* only, and the third statement refers to the contribution of breastfeeding to *all vertically transmitted* HIV infections.

Interpretation of the data has also been influenced by limitations of the early studies on this issue. These limitations include small sample sizes; insufficient data collected on the type and duration of breastfeeding among study mothers; and the lack of a test (before PCR was available) that could determine HIV infection in infants under 12 to 15 months of age.

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Later studies have overcome some of these weaknesses and have left no doubt that transmission can occur to infants through breastfeeding. However there are several major questions that remain unresolved in the HIV-breastfeeding relationship. These questions include:

- What are the precise risks of HIV transmission through breastfeeding, and how do these compare with risks of morbidity and mortality from *not* breastfeeding (and following different alternative feeding options) in various developing-country settings?
- What factors related to the mother, the infant, and the composition of breastmilk affect the risk of HIV infection through breastfeeding?
- Is there an optimal period of breastfeeding (timing of weaning) that will maximize the benefits of breastfeeding while minimizing the risk of HIV transmission, and how does this optimal period vary with circumstances?
- Are there interventions that could minimize the risk of HIV transmission through breastfeeding?
- What basic interventions and health services are required to minimize risks associated with *not* breastfeeding, and how can they be implemented and/or improved in resource-poor settings?

Answers to these important questions will facilitate the adaptation and application of the new UNAIDS/UNICEF/WHO guidelines on HIV and infant feeding in developing countries and will enable health workers to provide women with information and services to improve the health and survival of their infants.

This paper has five goals with respect to this important issue. These goals are to: 1) review the major advances in the study of HIV and infant feeding and the policy responses to these findings; 2) describe several issues to take into consideration when reading and comparing research studies on this issue; 3) report the findings of several studies and mathematical models that have been developed to guide program and policy recommendations; 4) summarize what existing studies do and do not reveal about this issue; and 5) recommend areas requiring further research to facilitate adaptation and application of existing guidelines on HIV and infant feeding. The paper is intended to inform program managers and others who are interested in learning more about HIV and infant feeding but who are not necessarily familiar with all of the technical issues in either of these fields.

II. Overview of Research Completed to Date

A. Chronology of Research Advances and Policy Responses

Interest in and availability of research on HIV and infant feeding grew dramatically in the period from 1985 to 1998, as health experts recognized the risks of HIV transmission through breastfeeding and the need to provide infant feeding guidance to women who are or might become infected with HIV. The major research findings and policy responses are described in **Box 1**. The general chronology is summarized on pages 3 and 4.

Between 1985 and 1989, incontrovertible evidence emerged that HIV is present in breastmilk. Documented cases of HIV transmission during breastfeeding by mothers who were infected postpartum were published, but the risk of HIV infection through breastfeeding was believed to be small. Nevertheless, HIV-infected mothers in industrialized countries (who were assumed to have safe alternatives to breastmilk) were advised not to breastfeed.

Between 1990 and 1994, new studies indicated clear evidence of HIV transmission through breastfeeding among women infected prior to delivery. However, the risk of postpartum transmission to infants through breastfeeding (as opposed to transmission occurring during pregnancy and/or delivery) could not be determined. Most studies carried out at this time compared total rates of mother-to-child transmission among children who were and were not ever breastfed. UNICEF and WHO urged continued support of breastfeeding in settings where infant diseases

Box 1:
Chronology of Research Advances and Policy Milestones

1985–1989: Evidence emerges that HIV is present in breastmilk. Documented cases of HIV transmission during breastfeeding by mothers who were infected postpartum are published, but risk of HIV infection during breastfeeding is believed to be small.

- Detection of HIV in breastmilk (Thiry et al, 1985).
- CDC advises U.S. women known to be HIV-infected not to breastfeed. Similar recommendations are issued in the U.K., Australia, and Brazil (CDC, 1985).
- Documented cases of HIV transmission associated with breastfeeding by mothers who were infected postpartum are reported in Australia (Ziegler et al, 1985), Rwanda (LePage et al, 1987), and France (Weinbreck et al, 1988). Researchers speculate that the high level of virus present in these recently infected mothers was responsible for the transmission and that mothers infected prior to delivery did not have the same risk of infecting their infants (Senturia et al, 1987).
- Vertical transmission via an HIV-seropositive wet-nurse with AIDS is documented (Colebunders et al, 1988).

1990–1994: New studies indicate clear evidence of HIV transmission through breastfeeding among women infected prior to delivery. However, the relative risk of postpartum transmission to infants (compared with in-utero or intrapartum transmission) can not be determined.

- Several studies estimate the risk of HIV transmission through breastfeeding by comparing overall vertical transmission rates among formula-fed and ever breastfed infants (Ryder et al, 1991; Hutto et al, 1991; ECS, 1991; de Martino et al, 1992; Kind et al, 1992; Gabiano et al, 1992; Collareda et al, 1993; Datta et al, 1994; Simonon et al, 1994). Using this approach, the risk of HIV infection that is attributable to breastfeeding varies greatly among studies, ranging from 0 to 46 percent.
- A meta-analysis of studies conducted between 1988 and 1992 (four studies in which mothers acquired HIV postnatally in Africa and Australia; and five studies in which mothers acquired HIV prenatally in Europe, the U.S., Africa, and Australia) is undertaken. This meta-analysis estimates a breastfeeding transmission rate of 14 percent from mothers who were seropositive at the time of delivery and 29 percent from mothers who had primary infection during the postpartum period (Dunn et al, 1992).[1]
- A UNICEF/WHO consultation reviews available research and concludes that breastfeeding should continue to be protected, promoted, and supported in all populations, irrespective of HIV infection rates, but adds that in settings where infectious diseases are not the primary causes of death during infancy, pregnant women known to be infected with HIV should be advised not to breastfeed but to use a safe feeding alternative for their babies (WHO, 1992).
- The development of DNA genome detection by polymerase chain reaction (PCR) for the early and definitive diagnosis of HIV is a significant improvement over antibody tests (which could not detect infections in infants less than 12–15 months old). Standardized commercial kits for PCR increase its use in research and clinical settings (Dunn et al, 1995). However, PCR is still not sufficiently accurate for determining the exact timing of HIV transmission in infants less than 30 days of age (Owens et al, 1996).
- The first generation of mathematical models which estimate the impact of breastfeeding on HIV transmission in various settings are published (Kennedy et al, 1990 and 1992; Heymann, 1990; Hu et al, 1992; and Del Fante et al, 1993).

Note 1
These limitations include small sample sizes, short breastfeeding durations; and wide confidence intervals (16–42 percent) on the estimate for mothers infected after delivery; and for the risk estimates for mothers infected before delivery, all but one study was carried out in an industrialized country, the precise timing of infant infection was not determined, the ever and never breastfed groups may not have been comparable or representative, and the one study carried out in Africa had only ten never breast-fed infants and no cases of infant HIV in that group.

Box 1 (con't): Chronology of Research Advances and Policy Milestones

- A study in Côte d'Ivoire indicates that the rate of perinatal transmission of HIV-2 (1.2 percent) is much lower than the rate of perinatal transmission of HIV-1 (24.7 percent) (Adjorlolo-Johnson et al, 1994).
- Standard definitions to describe the timing of mother-to-child transmission are proposed (Dabis et al, 1994).
- A clinical trial in the U.S. with the ACTG 076 protocol (which includes antenatal AZT from 24 weeks gestation, intravenous AZT during labor, and oral AZT to the infant for six weeks after delivery) reduces mother-to-child transmission of HIV by 67 percent in non-breastfed infants (Conner et al, 1994).

1995–present: Larger studies using new HIV detection technologies and sophisticated analytic methods focus more intensively on the role of breastfeeding in mother-to-child transmission. Studies estimate the effects of breastfeeding on the risk of late postnatal HIV transmission.

- Studies in Côte d'Ivoire (Ekpini et al, 1997) and the former Zaire (Bertolli et al, 1996) conclude that breastfed infants of HIV-1-infected mothers who escape early infection remain at risk of HIV transmission after six months (4 percent in Zaire; 12 percent in Côte d'Ivoire). In Côte d'Ivoire, the risk increased to 20 percent among infants who were breastfed for at least 24 months.
- Several researchers and mathematical modelers suggest that early weaning (estimates ranging from ages three to nine months) should be explored as a possible intervention to reduce HIV transmission through breastfeeding.
- UNAIDS, UNICEF, and WHO release a new statement on HIV and infant feeding which defines the elements required for establishing a policy in this area. These include supporting breastfeeding; improving access to HIV counseling and testing; ensuring informed choice [about infant feeding methods]; and preventing commercial pressures for artificial feeding (UNAIDS, 1997).
- International and local media in several countries begin reporting published and unpublished data on risks of HIV transmission through breastfeeding. At some international meetings governments and donors are urged to take action, including recommendations to subsidize infant formula for HIV-infected women and universal access to voluntary and confidential HIV counseling and testing. Public and private concern about the impact of inaccurate information on breastfeeding practices among non-infected women is raised.
- A meta-analysis of late-postnatal transmission using data from four longitudinal studies in industrialized countries and four studies in developing countries estimates the risk of HIV transmission through breastfeeding after three months of age at about three per 100 child-years of breastfeeding (Leroy et al, 1997).
- Clinical trials carried out in Thailand confirm that a short course of AZT given late in pregnancy and at the time of delivery can reduce HIV-transmission in non-breastfeeding women by half (CDC, 1998). Findings suggest that women who are given AZT for this purpose should also be provided with safe breastmilk substitutes and the Thai government takes steps to operationalize these guidelines.
- UNAIDS, UNICEF, and WHO prepare a background paper on HIV and infant feeding (1998a) and guidelines for decision-makers, and health care managers and supervisors (1998b and c). These organizations begin planning pilot projects to make breastmilk alternatives and/or antiretroviral therapy available to women in developing countries who are HIV-seropositive.

were the primary cause of infant deaths, regardless of HIV status.

From 1995 to the present, additional studies using new HIV detection technologies focused more intensively on the role of breastfeeding in mother-to-child transmission. Studies began estimating the risk of postnatal HIV transmission attributable to breastfeeding. With more information, the demand for policy and program guidance on HIV and infant feeding for developing country women increased. In early 1998, a study undertaken in Thailand demonstrated that a short-course of AZT administered late in pregnancy and at the time of delivery reduced mother-to-child transmission by about 50 percent in mothers who did *not* breastfeed (CDC, 1998).[2] The dramatic results of this study focused attention on the need to increase access to and availability of HIV counseling, testing, and antiretroviral therapy for women in the developing world. The findings also highlighted the need to reduce HIV transmission associated with breastfeeding, either by assuring access to replacement feeding[3] or by finding ways to make breastfeeding safer for HIV-seropositive women.

UNAIDS, together with UNICEF and WHO, commissioned a background paper on HIV transmission through breastfeeding (1998a) and prepared two sets of guidelines, one for decision makers and the other for health care managers and supervisors (1998b and c). The guidelines provide information about planning and implementing appropriate services to respond to the infant feeding-related needs of HIV-seropositive mothers, HIV-seronegative mothers, and mothers of unknown HIV status. Today, programs are beginning to seek ways to implement these guidelines, and pilot projects to provide short-course AZT treatment and/or replacement feeding to mothers with HIV and their infants are being planned.

B. Issues in the Design and Interpretation of Research Studies

Before discussing specific findings from studies, several issues that should be considered when reviewing and interpreting studies of HIV and breastfeeding are useful to mention. In addition to usual concerns, such as study design, sample size and power, sampling methods, measurement accuracy, and control for potential confounding variables, there are issues related to the diagnosis and timing of HIV transmission; the definition and measurement of breastfeeding practices; and generalizability of findings across populations that should be considered. These issues are discussed briefly below.

Measurement of HIV Infection and Timing of Transmission in Infants

Early in the epidemic, antibody tests to determine the HIV status of infants, such as the enzyme-linked immunosorbent assay (EIA or ELISA) with confirmation by Western Blot, were inconclusive in infants less than 12 to 15 months of age because of the tests' inability to differentiate between maternal and infant antibodies.[4] In the research context, studies of vertical transmission had to wait until infants were about 15 months of age to confirm HIV infection, and researchers did not know if the infant had been infected in-utero, intrapartum, or during the postpartum period.

The introduction of polymerase chain reaction (PCR), viral culture, and p24 antigen tests has largely overcome this problem because these tests are able to detect the virus itself rather than simply antibodies to the virus. The use of these new tests has allowed investigators to confirm more accurately infection in infants before 15 months of age, and to estimate the timing of transmission *after* the age of two or three months.

Where these new tests are not adequate, unfortunately, is in the determination of the precise timing of transmission in the infant in the first two months of life. For infants who test positive at birth or during the neonatal period, it is not possible, even with PCR, to determine whether transmission occurred in-utero, during delivery, or in the first weeks of life through breastfeeding. On the other hand, infants who test negative at birth and seroconvert during the first few weeks of life may actually have been infected during

Note 2
A more complicated Zidovudine protocol known as ACTG076 had already proven its effectiveness at reducing mother-to-child transmission in non-breastfed infants in the U.S. by 67 percent (Conner et al., 1994).

Note 3
Replacement feeding refers to the process of feeding a child not receiving any breastmilk from birth to about two years of age with a diet that provides all the nutrients a child needs. It is not limited to infant formula only.

Note 4
Maternal antibodies may still be present in infants' blood until twelve to fifteen months of age. After this age, HIV antibodies detected in an infant's blood are the infant's own antibodies and reflect their own HIV infection.

delivery, and it is not possible to assume that transmission occurred after birth through breastfeeding. A meta-analysis of existing studies that examine the sensitivity and specificity of PCR confirms that it is less accurate for neonates (under 30 days of age) than for older infants, children, and adults (Owens et al, 1996).

Determination of the timing of transmission during initial weeks of life is critical to determining the exact risks of transmission through breastfeeding, and our inability to determine the mode of infection at this age remains one of the major constraints to furthering our understanding of the HIV and breastfeeding relationship. Determining the timing of transmission is also important if early weaning is to be evaluated seriously as an option to enable HIV-infected mothers and infants to experience the benefits of breastfeeding in the early months, while avoiding transmission risk in later months, as has been suggested.

In the absence of methods for precisely determining the timing of early transmission, studies have made various assumptions in order to attribute transmission to the intrauterine, intrapartum, and postpartum periods, depending on the point at which a positive test result on an infant was actually found. These assumptions have tended to be conservative. Investigators in two recent studies suggest that their findings may underestimate the risk associated with breastfeeding, since they considered only children who initially tested negative, then were found HIV-seropositive after six months of age, to have been infected through breastfeeding (Ekpini et al, 1997; Bertolli et al, 1996). In these studies, some infants categorized as having been infected in-utero or intrapartum may actually have been infected through breastfeeding.

In order to improve comparability among studies, the Working Group on Mother-to-Child Transmission of HIV recommended standard definitions to describe the timing of mother-to-child transmission, as follows (Dabis et al, 1994):

- *In-utero*—the first positive viral marker is detected in the first two days of life.
- *In-utero plus intrapartum*—the first positive viral marker is obtained between 30 and 60 days of life.
- *In-utero plus intrapartum plus early postnatal*—the first positive viral marker is obtained between 90 and 180 days of life.

There is no standard definition of postnatal transmission through breastfeeding although some researchers have used a first positive viral marker after 180 days of life as indicative of transmission through breastfeeding. However, a recent meta-analysis defined late postnatal transmission as new infections acquired after three months of age (Leroy et al, 1997).

Other issues that complicate comparisons between studies include variations in the length of follow-up and differences in methods used to account for missing data, deaths, and children of indeterminant infection status. Studies that estimate transmission due to breastfeeding require repeated follow-up testing to determine the infection status of infants over time. These studies require mothers to bring infants back for testing at frequent and regular intervals. Invariably some mothers are unable to comply, and infants either have incomplete data or are lost to follow-up.

Not all researchers report on losses to follow-up or clearly indicate how they handle missing data and losses in their analyses and estimations of transmission rates. In some cases, studies only report their findings on infants who have survived into the second year of life. The length of the follow-up period, as well as the ways that investigators handle infants with uncertain diagnoses (due to missing data or loss to follow-up) can affect population estimates of mother-to-child transmission rates by as much as 40 percent (e.g., Pitt et al, 1998; Dabis et al, 1995).

Measurement of Breastfeeding Patterns and Practices

None of the studies published to date on HIV transmission and breastfeeding have explored differences in transmission associated with variations in breastfeeding practices.[5] In most early studies, mothers

simply are categorized as breastfeeding or not breastfeeding, or infants are categorized as ever and never breastfed, and total rates of mother-to-child transmission are compared between groups. Later studies examined the risk of HIV transmission by breastfeeding duration, but risks associated with different types and intensities of breastfeeding have not been studied explicitly.

Breastfeeding researchers typically distinguish between exclusive (no other liquids or solids except medicines are consumed), full (non-nutritive liquids are consumed), partial (other liquids, milks, and solid foods are consumed), and token breastfeeding (infrequent and for comfort only) (Labbok and Krasovec, 1990). These practices are associated with different risks of gastrointestinal and other infections in early infancy (Dewey et al, 1995; Launer et al 1990; Brown et al, 1989; Wright et al, 1989). Different breastfeeding practices influence the total amount of breastmilk consumed, the absorption of various nutrients, as well as patterns of infant growth (Victora et al, 1998; Piwoz et al, 1996; Dewey et al, 1989). Breastfeeding practices also affect lactational amenorrhea and the duration of postpartum infertility (Gray et al, 1990).

Variations in breastfeeding patterns may be important in studies of HIV transmission for several reasons. Some experts speculate that risk of HIV transmission may be lower when exclusive breastfeeding is practiced. This hypothesis suggests that HIV is more likely to pass through the infant's gut wall when it is disturbed (as happens when solids are introduced prematurely or when pathogens are introduced through unhygienic preparation). This hypothesis follows from studies showing an increased risk of sexually-transmitted HIV associated with disruption of vaginal mucous membranes, but it remains untested (Ruff, 1994).

Although exclusive breastfeeding is considered the ideal practice for infants up to about six months of age, in reality this behavior is practiced rarely. Therefore, studies of HIV and breastfeeding usually are comparing the transmission risks associated with mixed feeding (breastfeeding plus other liquids and/or solids) with the risks associated with limited or no breastfeeding. The role of other foods and liquids in modifying these risks has not been studied.

Another important breastfeeding practice that has been theorized to affect transmission relates to the consumption of colostrum. Colostrum contains high concentrations of cells, immunoglobulins, and other anti-infective proteins. Cell-associated HIV DNA has been found in colostrum samples taken from HIV-seropositive women. As a result, some researchers have speculated that colostrum consumption may increase the risk of HIV transmission because of its high concentration of cells (possibly containing viral DNA) consumed at a vulnerable time, when the newborn has a relatively immature immune system. This theory cannot be proven because the source of infection cannot be established at this age and it is presently unknown whether the HIV DNA is infectious and responsible for early postnatal transmission. Other experts suggest that the high concentrations of lymphocytes, macrophages, immunoglobulins, and other immune proteins in colostrum may actually protect against transmission, making early breastmilk less infectious than mature milk (Newell et al, 1997; Ruff et al, 1992).

Several researchers have attempted to correlate the presence and quantity of HIV (DNA, RNA, and p24 antigen) in breastmilk samples with risk of transmission through breastfeeding (Lewis et al 1998; Guay et al 1996; Nduati et al, 1995; Ruff et al, 1994) but results are inconsistent. Establishing this relationship is difficult for several reasons. For example, the pattern of viral shedding in breastmilk is uncertain. If virus shedding is intermittent, it is difficult to be sure that results obtained from milk collected at any given point in time are representative of the presence and concentration of virus in that woman's breastmilk over longer periods (Ruff, 1994). Furthermore, researchers are adapting tests developed for blood specimens to determine the presence of HIV in breastmilk. The sensitivity of these tests

Note 5
Only one study (Bobat et al, 1997) was found that reported differences in HIV-1 transmission by breastfeeding practices. However, this study did not use standard breastfeeding definitions. The authors report transmission rates among exclusive breastfeeders (in this study these are infants who consume breast-milk and no other milks); mixed feeders (infants who consume breastmilk and formula); and formula feeders (infants who consume formula only). All infants, including those who were classified as exclusively breastfed, consumed other liquids and solid foods for varying periods.

with breastmilk, which generally has a lower concentration of cells and HIV than plasma, is uncertain.

Generalizing Research Findings

Many studies of mother-to-child transmission of HIV have been carried out in Europe and the U.S. However, results of studies of HIV and breastfeeding that are carried out in industrialized countries may not be relevant to women in developing countries because of differences in breastfeeding practices, as well as differences in conditions that might affect the transmission of HIV through breastfeeding (e.g., maternal nutrition, infectious diseases, untreated infections).

Studies of HIV and breastfeeding in these countries also may have sampling biases that limit the generalizability of their results. For example, it is difficult to find large study populations of HIV-infected breastfeeding women in industrialized countries because breastfeeding is relatively uncommon in many countries. Women who do breastfeed usually do so for a relatively short period. In most industrialized countries, HIV-infected women now are specifically advised not to breastfeed to protect the infant from becoming HIV-infected through breastmilk. Therefore, studies that encourage HIV-infected research subjects to breastfeed are considered unethical in these settings. In contrast, in developing countries, breastfeeding is common practice (often for long durations), so it is often difficult to find a large control population of HIV-infected mothers who do *not* breastfeed for comparisons. In these observational studies, the small number of mothers choosing a particular feeding method may amplify the potential for bias due to self-selection.

C. Summary of Major Completed Studies in Developing Countries

Below is a review of five published studies from Côte d'Ivoire, Kenya, Rwanda, Tanzania, and the Democratic Republic of the Congo (formerly Zaire) that looked specifically at the relationship between HIV transmission and breastfeeding. These studies used reliable HIV tests to determine infection in infants; a specific definition of postnatal transmission; and analytic methods to account for losses to follow-up, some confounding variables, and other potential sampling biases. Characteristics and findings of the studies are summarized in **Table 1** and discussed below.

General Observations

All five studies were undertaken in African cities with relatively high seroprevalence levels in pregnant women, ranging from approximately five percent in Kinshasa to approximately 25 percent in Kigali. These are also cities in which breastfeeding is the norm, and breastfeeding beyond the second year of life is common. In all the studies, data on infants were collected between 1989 and 1994. Sample sizes (for the analyses reported) varied from 139 to 261 infants born to HIV-infected mothers. All were longitudinal, observational studies—none were clinical trials.

Objectives

The five studies attempted to estimate the risk of HIV transmission through breastfeeding, and most of them attempted to compare this risk of transmission with the risks of transmission in-utero and intrapartum. The Rwanda study had a second objective to evaluate PCR as a diagnostic tool for pediatric HIV infection.

HIV Tests Used and Definitions of Timing of Transmission

The five studies used different combinations of HIV tests and different intervals of testing to determine HIV status of infants studied, and different assumptions about the timing of transmission, making comparison of results problematic. Researchers also differed on their interpretation of the sensitivity and specificity of the PCR test, but there was consensus that the PCR was not as reliable in the first month of life (when both false negatives and false positive results could occur).

Investigators in Côte d'Ivoire, Tanzania, and the former Zaire determined rates of late postnatal transmission by classifying infants who had negative PCR results before about six months followed by positive results (PCR and/or serology) after this age as

infected through breastfeeding (see **Table 1**). As mentioned previously, this method may have underestimated HIV transmission through breastfeeding (Ekpini et al, 1997; Bertolli et al, 1996).

Investigators in Rwanda used two schemes to estimate the timing of HIV infection. The first approach assumed that all HIV-infected children who had a positive PCR test result on cord blood were infected in-utero, and those with a negative PCR on cord blood acquired infection either during delivery or postpartum. The second approach assumed that only children with a positive PCR result obtained after three months of age were infected postnatally.

The Kenya study specifically did not address the timing of transmission (Datta et al, 1994). In this study, investigators compared rates of mother-to-child transmission of HIV among infants surviving at least 12 months according to duration of breastfeeding. In these analyses, infants were classified as persistently seropositive, seroconverting during the postnatal period after a nine-month period of seronegativity, and uninfected. Infection status was determined by ELISA with confirmation by immunoblot.

Determining Causation of Late Postnatal Transmission

These studies used a variety of methods to confirm that postnatal transmission occurring in study infants was due to breastfeeding, as opposed to other means of contact with infected blood (such as transfusions, injections with unsterile needles or syringes, circumcision, or scarification).

- The Côte d'Ivoire, Kenya, and Tanzania studies followed a control group of infants who were breastfed by HIV-seronegative mothers. None of the control infants seroconverted during the study.
- The Kenya, Tanzania, and Zaire studies offered medical care to study infants to help insure that they did not receive contaminated injections elsewhere. Researchers also monitored the incidence of other potential risk factors, such as medical care given outside the study setting, circumcision, and scarification.
- Studies in Côte d'Ivoire and Kenya monitored duration of breastfeeding, and the Côte d' Ivoire researchers adjusted its estimates for patterns of weaning. Researchers in both of these studies observed a correlation between infant HIV infection and breastfeeding duration.

Major Findings and Interpretations

Since the studies all set out to measure somewhat different variables, the results are not easily comparable. However, highlights of major findings include the following:

- The total reported vertical transmission rates in these studies ranged from about 25 percent in Abidjan, Kigali, and Kinshasa to just over 40 percent in Nairobi.
- All five studies confirmed the occurrence of postnatal transmission of HIV. The risk attributable to breastfeeding (late postnatal transmission) ranged, on average, from about four to twelve percent, with higher risks if breastfeeding was sustained into the second year of life.[6]
- Investigators concluded that most, if not all, of the postnatal transmission among study infants was likely to have occurred through breastfeeding (and not transfusions, injections, or other exposures to HIV-infected blood).
- Investigators in studies in Côte d'Ivoire, Kenya, Zaire, and Rwanda considered the risk of HIV transmission through breastfeeding to be "significant."
- The Côte d'Ivoire and Kenya studies concluded that breastfed children are at higher risk of transmission if their mothers became infected *after* delivery.
- Authors of the Rwanda study concluded categorically that the potential benefits of breastfeeding still outweigh the risk of HIV transmission. The other researchers were more cautious in their interpretations.
- Studies in Côte d'Ivoire, Rwanda, and the former Zaire concluded that the inability of HIV tests to distinguish between intrapartum and early postpartum transmission through breast-

Note 6
Increased risk of postnatal infection through breastfeeding was reported after 12, 15, and 24 months of exposure in Tanzania, Kenya, and Côte d'Ivoire, respectively.

feeding, and the conservative adjustments they made in their data analysis to compensate for this, are likely to have led to an underestimation of breastfeeding transmission.

- In the Côte d'Ivoire study, no late postnatal transmission occurred in infants born to the 122 mothers infected with HIV-2 alone (as opposed to mothers infected with HIV-1, or dually infected with HIV-1 and HIV-2). This study strongly suggests that HIV strain is an important factor influencing risk of virus transmission through breastfeeding.
- Three studies concluded that early weaning should be explored as a possible recommendation for HIV-seropositive mothers since the risk of transmission continues throughout the duration of breastfeeding, while the full spectrum of benefits of breastfeeding diminish over time.

D. Summary of the Major Mathematical Models

In the absence of optimally-designed studies involving human subjects, several researchers have designed mathematical models to help policymakers and health program staff estimate the risk of HIV transmission from breastfeeding versus the risk of mortality from not breastfeeding (i.e., artificial feeding) and to use these estimates to formulate guidelines relevant for their populations. This section reviews seven major models that were published between 1990 and mid-1998. The models are described in greater detail in **Table 2**.

Before describing these models it is important to reiterate the limitations to modeling HIV transmission risk due to gaps in existing information. These gaps include:

- Data on the age-specific relative risks of mortality among exclusively breastfed, partially breastfed, and non-breastfed infants are very limited (presently there are only a few studies that estimate mortality risk by breastfeeding pattern and age, after adjusting for confounding variables);
- The possible benefits of breastfeeding beyond reducing risks of morbidity and mortality (e.g., for child spacing or other long-term benefits) are not included in any models;
- The additional risk of HIV infection that comes with increasing breastfeeding duration (i.e., exposure) is unknown and therefore impossible to model accurately;
- The effects of lactation on maternal nutritional status and immune competence (and how these subsequently affect transmission of HIV through breastfeeding) are also unknown and not possible to account for in models;
- Existing studies show a very wide range of vertical transmission rates and many of the factors that account for these variations are unknown and therefore cannot be added to these models; and
- Several of the models assumed that women know their HIV status, which is rarely the case in developing countries because of limited counseling and testing services.

In spite of these gaps, the models described are useful for understanding the ranges of risk associated with various conditions and settings and for illustrating how risk varies with changes in different assumptions and facts. Models also can be used to estimate the adverse effects on child mortality that may occur when HIV-seronegative women choose not to breastfeed (also called "spillover" mortality effects).

All of the mathematical models reviewed assumed that the alternative risks of mortality from unsafe feeding practices were significant in developing countries, and therefore none of the models advocated overall cessation of breastfeeding for an entire population because of the danger of HIV transmission through breastfeeding. Authors of three models (Nagelkerke et al, 1995; Del Fante et al, 1993; and Hu et al, 1992) explicitly endorsed the 1992 WHO/UNICEF policy that recommends that in the absence of safe alternatives, HIV-seropositive women should be encouraged to breastfeed. The authors of one model

(Kuhn and Stein, 1997) concluded that as long as the baseline infant mortality rate is not greater than 100 per 1000 live births, the best scenario occurs if no seropositive women breastfeed, and all seronegative women breastfeed optimally.[7] In contrast, Del Fante et al (1993) estimate that under five mortality will increase if all HIV-seropositive women do not breastfeed because a relatively large portion of infants who would not become infected by their mothers (about 70 percent) would be exposed to the risks of artificial feeding.

The models by Kuhn and Stein (1997) and Nagelkerke et al (1995) specifically address the alternative of breastfeeding initiation with early weaning for known HIV-infected mothers. These models assume that at a certain point in time the increased risk of HIV infection from prolonged breastfeeding may exceed the mortality-protection benefits. On the basis of their assumptions, Kuhn and Stein suggest that weaning at three months of age may be advantageous, and Nagelkerke et al suggest weaning between three and seven months.

USAID's LINKAGES Project has also developed a model for examining the effects on infant mortality of breastfeeding versus artificial feeding among mothers with and without HIV living under different conditions and that is not yet published (Ross, 1998). Similar to other models, this model allows users to manipulate the risk assumptions associated with different feeding decisions in order to estimate critical values (or cut-off points) below or above which decisions about the advisability of breastfeeding in the presence of HIV will change.[8] The spillover effects on child mortality can also be estimated.

The LINKAGES model confirms the conclusions of the other mathematical models cited above—in populations with high levels of infant mortality (usually due to infectious diseases), the risk of child death is lower if mothers with HIV breastfeed their infants. A switch to artificial feeding at some time during infancy reduces mortality risk, but the optimum timing of the switch depends on the conditions assumed.

For example, in a population where it is assumed that 1) infant mortality is 100 per 1000 live births; 2) the relative risk of mortality due to artificial feeding is 3.0; and 3) 16 percent of infants born to HIV-seropositive mothers who are uninfected at birth become infected through breastfeeding, the policy to promote breastfeeding among all women (without regard to their infection status) will result in fewer child deaths. However if any *one* of the following critical values is reached, then more child deaths will be experienced when HIV-seropositive women breastfeed: 1) infant mortality is lowered to 74 per 1000 live births; 2) the relative risk of death from not breastfeeding is 2.4 (instead of 3.0); or 3) HIV transmission attributable to breastfeeding is 22 percent[9] (instead of 16 percent). These conditions may be encountered in some populations and/or at some infant ages.

III. Conclusions and Discussion

This review has identified areas of consensus and gaps in our knowledge about HIV transmission through breastfeeding. These issues and recommendations for future research on this issue are summarized below.

A. What We Know

There is general agreement on the following points:

- **Advantages of breastfeeding.** There are significant health, nutritional, psychological, and social advantages of breastfeeding for both mother and infant. Breastfeeding reduces the risk of infant morbidity and mortality and increases birth spacing, especially in developing countries.
- **HIV transmission through breastmilk.** HIV has been detected in the breastmilk of infected mothers, and HIV can be transmitted by breastfeeding to infants of mothers who were themselves infected before, during, or after pregnancy.
- **Timing of mothers' transmission.** Mothers who become infected with HIV postnatally (while they are breastfeeding) are

Note 7
The authors defined optimal breastfeeding as exclusive breastfeeding to age four to six months and breastfeeding supplemented with other foods for 12 months or longer.

Note 8
The key variables that are manipulated include baseline mortality rates, the risk of HIV transmission through breastfeeding, and the relative risks associated with not breastfeeding (which can vary with local conditions or as a result of programs to reduce these risks).

Note 9
This value is the upper limit of the Dunn et al (1992) 95% confidence interval for HIV transmission attributable to breastfeeding in women infected prenatally and the upper limit of the Bertolli et al estimate for late postnatal transmission.

more likely to infect their infants through breastfeeding than mothers who are infected before delivery because of the high viral load immediately following infection. By the same reasoning, it is also generally agreed that mothers with AIDS (and a high viral load) are also more likely to transmit the virus through breastfeeding.

- **Low risk of transmission of HIV-2 through breastmilk.** Infants of mothers infected with HIV-2 are less likely to be infected through breastfeeding than infants of mothers infected with HIV-1. However, there are relatively few areas where women are infected exclusively with HIV-2.

B. What We Do Not Know

There is limited speculation, hypotheses, evidence, and/or scientific knowledge, but no definitive answers or consensus on the issues listed below.

- **Relative risks of alternative feeding methods.** Data are limited on the age-specific risks of morbidity and mortality in infants who are not breastfed, optimally breastfed (including exclusive breastfeeding for about the first six months), and/or given mixed-milk feeding—irrespective of the HIV status of the mother.
- **The possible risks and benefits of early weaning.** Three studies and at least two mathematical models conclude that the benefits of breastfeeding for infants of HIV-infected mothers may exceed the risks of artificial feeding *only* in the first months to a year of life. However, these studies were not designed to identify an optimal age for early weaning. Such a recommendation will vary by setting, depending on the safety and quality of appropriate replacement foods. To date, no studies or models have directly taken into consideration the nutritional quality of the replacement diet (particularly the foods other than breastmilk substitutes or artificial milks) when evaluating the risks and benefits of not breastfeeding or early weaning with HIV.
- **Maternal characteristics and behaviors that influence transmission of HIV through breastfeeding.** Known maternal risk factors for perinatal HIV transmission include high viral load, reduced maternal CD4 cell counts, quality of immune response, stage of maternal disease, low maternal serum retinol concentration, and breastfeeding (Semba et al, 1994; Nduati et al, 1995; Scarlatti, 1996; John and Kreiss, 1996; Newell et al, 1997). Other maternal characteristics that are suggested to increase HIV transmission risk include mastitis, cracked nipples, and breast abscesses in an infected, breastfeeding mother (Nicholl, 1995; Newell et al, 1997), as well as early membrane rupture, duration of labor, poor nutrition, concurrent sexually transmitted diseases, and other infections, such as placental malaria parasitemia during pregnancy.

  Trials are underway to evaluate whether micronutrient supplementation can reduce vertical transmission overall, and whether some nutrients, such as vitamin A, can reduce transmission through breastfeeding. At present, it is not known whether vitamin supplementation, or stopping breastfeeding when breast nipple integrity is compromised or breast symptoms occur, will effectively reduce HIV transmission through breastfeeding. It is also suggested that specific behaviors, such as heat treatment of expressed breastmilk, will reduce viral activity and transmission (Black et al., 1996), but the feasibility and impact of this practice have not been evaluated. There is also little or no information on the effect of lactation on the immune systems of HIV-infected mothers, and whether breastfeeding itself compromises or protects infected women from worsening health and nutrition status.
- **Infant characteristics that influence risk of HIV transmission through breastfeeding.** Studies have not yet identified specific infant characteristics that affect their susceptibility to HIV-infection through breastfeeding, and more research is needed in this area. Among those traits hypothesized to affect trans-

mission are prematurity and low birth weight (John and Kreiss, 1996), which affect immune system development; oral mucosal integrity and lesions (Newell et al, 1997); diarrheal and other diseases that affect intestinal gut integrity and permeability (Ruff, 1994); and teething (Datta et al, 1994). The possibility that HIV-infection is the cause rather than the effect of some conditions must be considered in studies of these possible risk factors.

- **The effects of antiretroviral therapy on HIV transmission through breastfeeding**. Clinical trials carried out in Thailand suggest that a short course of AZT given late in pregnancy and at the time of delivery reduces HIV-transmission by half in non-breastfeeding women (CDC, 1998). No data are currently available to indicate the potential effect of antiretroviral therapy on HIV transmission through breastfeeding although studies are underway. There is some concern that antenatal AZT treatment may actually increase viral load during breastfeeding, reducing its overall efficacy in breastfeeding populations.[10]
- **The role of colostrum in HIV transmission through breastfeeding.** Determining whether infection takes place through cell-free HIV in breastmilk or through HIV-infected cells is important for assessing the role of colostrum in HIV transmission. Researchers have not determined if colostrum protects the infant from HIV acquisition, or instead, through a high concentration of virus, colostrum puts infants at heightened risk.
- **Psychological and social consequences of the transmission of HIV through breastfeeding**. There is virtually no information on the psychological and social consequences of the HIV-infant feeding dilemma. For example, it is unknown what toll the fear of infecting an infant through breastfeeding—a practice with deep evolutionary, cultural, and emotional roots—takes on women, families, and society. Furthermore, the impact of counseling about breastfeeding risks and alternative feeding methods has also not been studied systematically.

Note 10
It has been theorized that short course AZT therapy might actually increase the risks of HIV transmission during breastfeeding. This theory is based on observations of a spiking or rebound effect on viral load in some adults after the cessation of AZT given for therapeutic purposes. Cessation of AZT (given for the prevention of perinatal transmission) occurs immediately after delivery, when breastfeeding begins, and at a time when the newborn is considered to be vulnerable. The effects of AZT on breastmilk viral load over time are unknown.

Findings from the studies discussed in this paper have contributed significantly to our scientific and policy thinking on HIV and infant feeding. These studies have also helped formulate the UN agencies' recent guidelines (UNAIDS/UNICEF/WHO, 1998b and c). These guidelines support the notion of fully informed and free choice on infant feeding for all mothers by making voluntary counseling and HIV testing available and accessible (because women can only make informed decisions about infant feeding if they know their HIV status). The guidelines also recommend that breastfeeding should continue to be protected, promoted, and supported among HIV-seronegative mothers and among mothers of unknown HIV status. Mothers who are HIV-seropositive should be informed about the risks and options for feeding their infants. HIV-infected mothers who choose *not* to breastfeed are to be supported in their decisions and counseled about feeding options from birth to six months (including the preparation of suitable breastmilk substitutes) and from six months to two years of age (including suitable breastmilk substitutes and appropriate replacement foods).

However, both the adaptation of these guidelines to individual country or regional settings and to individual mothers and the successful application of the guidelines (resulting in actual improvement of mothers' ability to make optimal decisions about their feeding choices) will be compromised until answers are found to the questions raised in this paper. More specifically:

- The lack of information on the relative risks associated with alternative feeding methods and practices makes counseling about the risks of *not* breastfeeding and how they can be minimized, and decision-making by HIV-infected women about whether to initiate and/or continue breastfeeding extremely difficult.
- Early cessation of breastfeeding is recommended in the guidelines as one option for reducing the risk of transmission. However, the optimum time or circumstances for early wean-

ing in different populations has not been studied properly. The risk of HIV transmission associated with increasing breastfeeding duration is not known, further hindering useful counseling on this subject. The existing guidelines also provide very limited information on age-appropriate, non-milk replacement foods and feeding practices for infants older than six months of age, and they do not contain feeding advice for HIV-infected infants.

- The maternal and infant characteristics that affect HIV transmission through breastfeeding are not well understood. This limits health workers' ability to correctly advise HIV-seropositive women who breastfeed on selected signs or symptoms to watch for that might increase their risk of transmitting the virus through breastfeeding.
- The role of colostrum in HIV transmission is not known. If it is found to increase the risk of HIV infection during breastfeeding, mothers might be advised to withhold colostrum (although it is probably difficult to determine, in practice, the difference between colostrum, transition milk, and mature milk; and alternatives to colostrum could pose their own risks). If it is not infectious, then early initiation of breastfeeding may protect rather than harm vulnerable infants.
- The paucity of information on women's perceptions of the links between HIV infection and breastfeeding, the potential for stigmatization of women who do not breastfeed, and other psychosocial factors limit health workers' ability to improve the quality of their counseling or the way they deliver specific messages. In addition, this information will be useful for developing strategies to avoid a "spillover" effect of replacement feeding for women who are HIV-seronegative or are of unknown status.

Proper implementation of the UNAIDS/UNICEF/WHO guidelines will require expansion and improvement of existing health services, with significant practical and financial implications for developing countries. These improvements include the introduction and expansion of voluntary, confidential HIV counseling and testing services; universal counseling on infant feeding; improvement of antenatal care services; strengthening of family planning services;[11] and an overall, comprehensive strengthening of health care services and programs (including HIV prevention for women and social support, among others). These services are often weak, and other interventions that are believed to reduce transmission among couples, such as treatment of sexually transmitted infections, are not yet being widely implemented or strengthened.

C. Future Research Priorities

This review has identified several unanswered questions related to the transmission of HIV and infant feeding. Some of these questions are listed in **Box 2**. Future research to address these questions can be divided into three categories:

1. Research to identify risk factors for HIV transmission through breastfeeding;
2. Research to test the efficacy and effectiveness (including costs, feasibility, and long-term impact) of different interventions to reduce transmission through breastfeeding; and
3. Research to improve the operations and quality of programs to address this issue (including training needs and approaches, supervision and follow-up strategies, social support requirements, among others).

This review has mainly addressed questions related to point 1, with limited discussion of point 2 priorities. However, there are many questions related to program operations and implementation (point 3) that also require immediate attention. These include questions such as:

- What are appropriate strategies for counseling HIV-seropositive women and their families about infant feeding (including timing; locations; providers; and affordable training, supervision, and follow-up strategies)?
- What are appropriate strategies for making replacement feeding available,

Note 11
Improving the availability, accessibility, and use of family planning services is an especially important intervention in this context. Women who do *not* breastfeed do not benefit from lactational amenorrhea, and are at risk of becoming pregnant soon after birth. These new pregnancies create additional opportunities for mother-to-child HIV transmission.

Box 2:
Unanswered Questions Related to HIV and Infant Feeding

Questions on risk factors:

- What are the actual risks of and risk factors for HIV transmission though breastfeeding under different conditions in various settings?
- What are the age-specific relative risks of morbidity and mortality associated with different feeding practices (in the absence of HIV) in different settings?
- What are the age-specific advantages and risks of early weaning of infants of HIV-infected mothers in different settings?
- In what settings and for which individual HIV-infected mothers, does the risk of sustained breastfeeding outweigh the risks of artificial feeding and/or early weaning?
- What maternal and infant characteristics affect the risk of HIV infection through breastfeeding (and do changes in them reduce transmission)?
- Do HIV-specific antibodies and other components of breastmilk affect the virus and risk of transmission?
- What is the impact of *not* breastfeeding on infected women's health, fertility, and vertical transmission to subsequent children?

Questions on the efficacy and effectiveness of interventions:

- Are there low-cost, affordable ways to reduce the risk of HIV transmission through breastfeeding?
- Are there specific, affordable interventions that can reduce the risks of HIV transmission through breastfeeding that do not require knowledge of a woman's HIV status?
- What basic interventions and health services are required to minimize risks associated with *not* breastfeeding, and how can they be implemented and/or improved in resource-poor settings?
- What is the cost, feasibility, and long-term impact of interventions to reduce HIV transmission through breastfeeding (such as voluntary antenatal counseling and testing and replacement feeding)?
- What are the effects of antiretroviral therapy (such as AZT) on the transmission of HIV through breastfeeding?

affordable, and safely practiced by HIV-infected women (for long periods of time to fully replace breastfeeding) while minimizing spillover, dependency on donor supplies, and adverse health and nutrition consequences in individuals and communities?

- How can access to and utilization of voluntary counseling and testing by pregnant women (and their partners) be improved so that women are able to make informed decisions about their reproductive health and infant feeding?
- How can women be empowered and supported in their decisions to take actions to prevent primary HIV infection as well as to prevent vertical transmission?

Finally, only limited attention has been paid to date to the systematic study of the impact of the HIV epidemic on infant feeding attitudes and decisions. Future research should include a better understanding of:

- Whether fear of transmission has already begun to affect infant feeding patterns among mothers who are HIV-seropositive and/or uncertain of their status;
- How health workers in various settings are presently counseling women who know or suspect that they are infected and that ask for advice on infant feeding, and what impact this has on their feeding decisions and their children's

subsequent health, growth, and development; and

- Whether women who avoid breastfeeding because they are worried about infecting their babies face stigmatization (by other family members and the community), rejection, and/or other negative psychological, physical, or economic consequences, and how these can be mitigated.

All studies of HIV and breastfeeding are likely to face ethical challenges in the future, given the fact that both encouraging study subjects to breastfeed (if they might be HIV-infected) or encouraging them to artificially feed (with its accompanying risks) could endanger their infants. Breastfeeding and HIV studies are likely to be subject to even more rigorous scrutiny than previously, given the recent controversy over the U.S.-funded studies on AZT therapy to prevent mother-to-child transmission of HIV in developing countries and other ethical considerations.[12] However, the successful adaptation and application of responsible policies and guidance on infant feeding in settings where women are at risk of HIV will be hindered until more is learned about the complex factors affecting infant feeding decisions and their impact on child survival in resource-poor settings. Until that time, women and the health workers who counsel, advise, and care for them will face immense challenges interpreting incomplete information and making the best decisions for themselves, their families, and their infants.

Note 12
These studies were criticized for giving placebos to a control group of women when the drug's efficacy had already been confirmed in earlier studies conducted in industrialized countries. Other ethical issues being discussed include whether it is ethical to give an infected mother a short-course therapy that only benefits her baby, and whether it is ethical to test treatments that are not likely to be affordable and widely available in study populations.

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Table 1: Major Studies on HIV and Breastfeeding in Developing Countries

Site, Author, Pub. Date, Sample Size, Type of Study	Objective	HIV Test(s) Used for Infants/ Children	Breastfeeding Definition(s) Used
Côte d'Ivoire Ekpini et al **Date**: 9/90–10/94 **Sample size for this analysis**: • 82 children born to HIV-1 positive mothers • 57 infants born to dually infected mothers (HIV-1 & HIV-2) • 30 infants born to HIV-2 positive mothers • all were breastfed • 39 were HIV-infected at the end of the follow-up **Study design**: Longitudinal, observational	To estimate the risk of HIV transmission through breastfeeding	EIA (HIV-1 and HIV-2) and PCR. Serology obtained at 1, 2, and 3 months of age, and every 3 months after that. Authors suggest that PCR techniques have sensitivity and specificity of 100%.	No specific definitions used or practices measured. The median duration of breastfeeding among children followed for at least 24 months was 20 months.
Kenya Datta et al **Date**: 12/90–12/92 **Sample size for this analysis**: • 220 children surviving for at least 12 months • all born to HIV-1 positive mothers • 90 children were HIV positive at the end of follow-up **Study design**: Longitudinal, observational	To study the frequency of, and risk factors for, mother-to-child transmission of HIV-1.	ELISA with confirmatory immunoblot Blood for serologic assays was collected at 6, 14, and 24 weeks; 9, 12, 15, and 18 months; and every 6 months thereafter.	Breastfeeding initiation was universal in the study population. Infants who survived for at least 12 months were classified according to whether they were breastfed beyond 15 months (yes/no). Risk associated with breastfeeding duration (in months) was also measured using Cox proportional hazards modeling.

CI = confidence interval
EIA = enzyme immunoassay
ELISA = enzyme linked immunosorbent assay
PCR = polymerase chain reaction

Definition(s) of Timing of Transmission	Major Findings	Interpretation
Early HIV infection (in-utero or intrapartum) was defined as a positive HIV-1 PCR obtained in first 6 months of life. Late postnatal infection was attributed to infants with a negative PCR at 3 or 6 months, followed by either or both positive HIV-1 PCR at 9 months or older, or persistently positive HIV-1 serology at 15 months or older. Analysis adjusted for losses to follow-up and for weaning.	Total vertical transmission rate was about 25%. 20% of children acquired HIV infection in first 6 months of life. 12% of all children of HIV-1 positive mothers who escape infection during first 6 months of life will become HIV-positive by 24 months. Late postnatal transmission is greater, 20%, among children breastfed for at least 24 months. No instances of late postnatal transmission were observed in infants of mothers infected with HIV-2 only. Rates of late postnatal transmission were 9.2 per 100 child years of breastfeeding among mothers infected with HIV-1 only, and 4.8 per 100 child years of breastfeeding for dually infected women.	Breastfed children born to HIV-1 positive or dually infected mothers in Abidjan are at substantial risk of late postnatal transmission. Most postnatal transmission is likely to have occurred through breastfeeding and not transfusions, injections, or other exposures to HIV-infected blood. Postnatal transmission may have been underestimated since some children with a positive PCR in first 6 months may have acquired the infection through breastfeeding. Breastfed children are at a higher risk of infection if mothers seroconvert during the postpartum period. Weaning at 6 months could reduce risk of HIV transmission through breastfeeding.
This study could not distinguish in-utero, intrapartum, from postpartum infection. However, infants were classified as HIV-1 (negative), persistently HIV-1 positive, and seroconverting (if HIV-negative for at least 3 months and then seroconverting). N = 130 (59%), 50 (23%), and 40 (18%), respectively for these groups.	Total vertical transmission was >40% in this study population. Breastfeeding duration was longer among surviving HIV-infected infants ($p < 0.05$). Average duration was 14 months in HIV negative, 15.9 months in persistently positive, and 17.5 months in seroconverting children. HIV positive children were 1.9 times more likely to breastfeed for 15 months or longer (95% CI: 1.1–3.5). Odds were 2.5 among seroconverting children ($p < 0.05$). A substantial proportion of HIV infection occurred postnatally, possibly through breastfeeding.	Investigators hypothesize that the high rates of vertical transmission in this study may result from longer periods of follow-up. They also suggest that some children may be protected from HIV-1 during first few months of breastfeeding, and studies with shorter follow-up periods may result in lower estimates. Mouth ulcerations and teething, which increase with age, may increase transmission risks over time. The increased risk of HIV transmission associated with prolonged breastfeeding (15 months or longer) may exceed the benefits for infants of HIV-1 infected mothers.

Table 1: Major Studies on HIV and Breastfeeding in Developing Countries

Site, Author, Pub. Date, Sample Size, Type of Study	Objective	HIV Test(s) Used for Infants/ Children	Breastfeeding Definition(s) Used
Zaire Bertolli et al. **Date**: 10/89–4/90 **Sample size for this analysis**: • 261 children of HIV-1 infected mothers • 69 children were HIV-positive at the end of the follow-up period • Average follow-up was 18 months **Study design**: Longitudinal; observational	To estimate HIV vertical transmission rates, and risks attributable to gestation; labor and delivery; the early postpartum period; and the late postpartum period (through breastfeeding).	Venous blood drawn at 0–2 days postpartum, and every 3 months thereafter for PCR and HIV culture.	Breastfeeding practices were not specifically measured. Investigators report a median duration of breastfeeding of 12 months in study children. Eleven children were either not breastfed (N = 9) or weaned before 3 months of age (N = 2).
Tanzania Karlsson et al. **Date**: 1991-not reported **Sample size for this analysis**: 139 children born to HIV-1 positive mothers who were uninfected at 6 months of age 8 children became infected, all after 11 months of age. **Study design**: Longitudinal; observational	To study the rates of late postnatal transmission of HIV-1 in children born to HIV-1 infected mothers.	PCR complemented with p24 antigen and HIV antibody tests. Infant blood samples were taken every 3 months. First sample was taken between 4–8 weeks. HIV infections status was determined when a child had at least 2 negative samples (test results) followed by 2 HIV-positive samples or 1 HIV-negative sample and subsequent death due to HIV-related disease.	Specific breastfeeding practices were not measured. Investigators report that "all women in the cohort were breastfeeding."

CI = confidence interval
EIA = enzyme immunoassay
ELISA = enzyme linked immunosorbent assay
PCR = polymerase chain reaction

Definition(s) of Timing of Transmission	Major Findings	Interpretation
In-utero transmission was assumed if the virus was detected in infant blood within 48 hours of birth. Intrapartum/early postnatal transmission was assigned if there was a negative PCR in the first 2 days of life, followed by positive result between 3–5 months of ages. Late postnatal transmission was assumed if there was a negative PCR result between 3–5 months, followed by (positive) PCR, antibody test, or HIV culture at a later age. Only 59% of children had sufficient data to determine the timing of transmission.	Overall vertical transmission rate was about 25%. Among the 69 HIV-positive children: • 23% were infected in-utero [95% CI: 14–35%]; • 65% were infected intrapartum or early postnatal [CI: 53–76%]; • 12% were infected late postnatally [CI: 5%–22%]. The risk of HIV transmission was: • 6% in-utero; • 18% intrapartum or early postnatal; • 4% last postnatal.	Risk of vertical transmission is greater during labor and delivery than during gestation. The risk of infection attributable to breastfeeding is "significant." The study's inability to distinguish between intrapartum and early postnatal transmission through breastfeeding most likely resulted in an underestimate of the risk of transmission associated with breastfeeding. A trial of early weaning or formula feeding is suggested by the investigators. Note: Children with missing test results were assigned to groups (to estimate transmission risks and proportions) according to the distribution of children without missing results. Children with indeterminant HIV status (N = 25) were not included in transmission estimates.
Late postnatal transmission was assumed if an infant born to an HIV positive mother was PCR negative at 6 months, and PCR positive after 6 months.	The overall vertical transmission rate in the study population was about 30%. Eight infants who were uninfected at 6 months became infected during the follow-up. Seven of these were breastfed at the time of infection (positive test result). Transmitting mothers had lower CD4 cell count counts than nontransmitting mothers. Not all infants were followed for the same period of time. Overall late postnatal transmission rate was about 6 per 100 child years of observation. No seroconversions occurred between 6–11 months.	Investigators suggest that 6–9 months may be the age after which the advantages of breastfeeding no longer exceed the risk of HIV transmission, but it is unclear how this recommendation emerged from the study.

Table 1: Major Studies on HIV and Breastfeeding in Developing Countries

Site, Author, Pub. Date, Sample Size, Type of Study	Objective	HIV Test(s) Used for Infants/ Children	Breastfeeding Definition(s) Used
Rwanda Simonon et al. **Dates**: 1988-not reported **Sample size used in the analysis**: - 188 children born to HIV-1 infected mothers - 47 children who survived to 15 months were HIV positive by 24 months - Follow-up was for 24 months - 40 children (not included in the 188) died in the first 24 months of life **Study design**: Longitudinal; observational	To estimate the proportion of HIV-1 transmission occurring in-utero, intrapartum, and postnatally. To evaluate PCR as a diagnostic tool for pediatric HIV infection.	EIA and double PCR at birth (cord blood), and at 3, 6–12, and 13–24 months of age. HIV infection in infants was diagnosed as follows: • AIDS diagnosed according to clinical criteria; • child died of AIDS-related disease before 15 months; or • HIV antibody positive at 15 months. Child was considered uninfected if: • HIV antibody negative at 15 months; or • lost to follow up or died of an unrelated cause and was HIV antibody negative at 9 months or older. All other children had indeterminant status (N = 32), including those who died during the neonatal period.	Breastfeeding practices were not measured or described. The median duration of breastfeeding was 579 days (range: 0–1302 days).

CI = confidence interval
EIA = enzyme immunoassay
ELISA = enzyme linked immunosorbent assay
PCR = polymerase chain reaction

Definition(s) of Timing of Transmission	Major Findings	Interpretation
Timing was based on two different sets of assumptions. Under the first assumption, all HIV-1 positive children with a (negative) PCR on cord blood were thought to be infected during delivery or birth. Under the second assumption, only children with a positive PCR obtained after 3 months of age were thought to be infected postnatally.	Total vertical transmission rate (at 24 months) was about 25%. Using the first assumption, the in-utero transmission rate was 7.7% and the intrapartum transmission rate was 17.6%. Using the second assumption, the in-utero and intrapartum transmission rate was 20.4% and the late postnatal transmission rate was 4.9%. 5% of cord blood samples produced false positive readings suggesting contamination with maternal blood. 8% false positive PCR result found in children from uninfected mothers. At 24 months, all HIV-infected children had at least 1 positive PCR result.	Investigators concluded that breastfeeding should continue to be recommended and promoted; however known HIV-1 positive mothers who can afford and are able to safely artificial feed may be counseled individually against breastfeeding. Results also suggest that the double PCR method is extremely sensitive. Cord blood is probably not suitable for early diagnosis of HIV-1 infection in newborns due to probable contamination with maternal blood.

Table 2: Major Mathematical Models of HIV Transmission and Breastfeeding

Author, Pub. Date	Objective	Unique Features And Major Assumptions	Major Findings and Interpretation
Ross/LINKAGES (unpublished)	To examine the effects on overall infant mortality of breastfeeding versus artificial feeding among mothers with and without HIV under different conditions/ assumptions.	Allows sensitivity analysis and identification of critical values for all important variables (breastfeeding rates, baseline infant mortality rate, transmission rate, and relative risk of death due to artificial feeding). By redefining age categories, the model can be used to predict outcomes for specific age periods within infancy.	Where infectious diseases are the main cause of infant mortality, the risk of death is lower if mothers with HIV breastfeed their newborn infants. A switch to artificial feeding sometime during infancy would reduce the infant's risk of death. Optimal timing of this switch depends on the conditions assumed.
Kuhn and Stein 1997	To examine the effects of optimal breastfeed-ing, complete avoidance of breastfeeding, and early cessation of breastfeeding, in the context of HIV.	Considers issue of duration of breastfeeding, and three different feeding practices. Assumes IMR < 100/1000 and relative risks of dying set at 2.5 for non-breastfed compared with optimally breastfed infants.	Avoidance of all breastfeeding by the whole population always produces the worst outcome. The lowest frequency of adverse outcomes occurs if no HIV-seropositive women breastfeed and all HIV-seronegative women breastfeed optimally. When it is not possible to distinguish individual from community risk (in the absence of HIV testing), sustained promotion of breastfeeding is most desirable. Early cessation of breastfeeding at 3 months of age for known HIV-infected mothers could be advantageous.
Nagelkerke 1995	To compare the age-specific risks of mother-to-child HIV transmission versus the excess mortality due to not breastfeeding.	Considers the issue of duration of breastfeeding. Assumes that both risk of mother-to-child transmission of HIV through breastfeeding and the relative risk of not breastfeeding do not vary with age. However, the benefits of breastfeeding decrease with age.	In HIV-1 seropositive mothers, the decrease in child mortality afforded by breastfeeding may exceed the risk of mother-to-child HIV-1 transmission only during the first 3–7 months of life (in many African settings). Thereafter, the risk of HIV-1 transmission probably exceeds the mortality reduction benefit of breastfeeding. Experimental studies on early weaning should be considered. Supports the WHO/UNICEF 1992 recommendation that in the absence of safe alternatives, HIV-1 infected women should be encouraged to breastfeed.

Table 2: Major Mathematical Models of HIV Transmission and Breastfeeding

Author, Pub. Date	Objective	Unique Features And Major Assumptions	Major Findings and Interpretation
Del Fante 1993	To evaluate the impact of HIV transmission and breastfeeding practices on under-5 mortality among HIV(+) and HIV(-) mothers living in urban and rural areas.	Model takes no account of the duration of breastfeeding. Assumptions of conditions were those of a hypothetical country in East Africa.	Childhood mortality would increase substantially if breastfeeding ceased. In urban settings, <5 mortality would increase by 27% among children born to HIV-1-infected mothers, and 108% among those born to uninfected mothers. In rural areas, mortality increases would be even more substantial. Adverse effects on mortality occur even if it is possible to restrict cessation of breastfeeding to HIV-infected mothers. Promotion of breastfeeding should continue regardless of HIV prevalence rates, as per WHO/UNICEF (1992) recommendation.
Hu 1992	To compare the mortality associated with HIV transmission through breastfeeding with the mortality expected from not breastfeeding in different populations, and to perform sensitivity analyses to illustrate critical boundaries for guiding research and policy.	Assumed there were no benefits of breastfeeding after one year.	Supports the 1992 WHO/UNICEF recommendation that breastfeeding should continue to be encouraged since, in most cases, it protects the majority of infants from mortality related to infectious diseases and malnutrition. Also supports the U.S. and U.K. recommendations that HIV-infected women in the U.S. and U.K. should not breastfeed.
Kennedy 1990	To compare the infant mortality associated with breastfeeding with that of not breastfeeding in a hypothetical population of 100,000 uninfected infants born to infected mothers	Assumes: • probability of HIV transmission by breastfeeding alone is probably quite low (<1%). • 95% of infected babies will die before age 5. • four different relative risks of death due to diseases of infancy for bottle-fed babies, compared to breastfed babies, are used.	The breastmilk transmission rate must be 20% before the expected number of deaths among breastfed babies approaches that associated with bottle feeding. However the modelers assume that the transmission rate is likely <1%. Encourages infected mothers to breastfeed until some basic questions about HIV and breastfeeding are answered.
Heymann 1990	To compare the survival outcomes of children born to HIV-infected women who are breastfed, bottle fed, and wet nursed.	Wet nursing is included as an "alternative feeding practice," although potential problems with this practice were mentioned. This models looks at outcomes of a range of values for HIV transmission through breastfeeding, HIV seroprevalence, positive predictive value of a screening test, the child mortality rate from non-HIV-related causes, and the HIV child mortality rate.	The probability of HIV transmission via breastfeeding would need to be at least 0.12 in a community with an <5 mortality rate from non-HIV causes of 100/1000 live births and at least 0.27 in a community with a rate of 210/1000 before alternative feeding practices should be recommended even to the known HIV-infected mother who has an available feeding alternative with a relative risk of 2:1.

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